REMARKS

The Pending Claims

Prior to entry of the above amendments, Claims 1-11, 13, 15, 17, 19, 20, 22-39, 43-45, and 47 are pending. Claims 1-11, 13, 15 are directed to a method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal or glial cell. Claims 17, 19, 20, 22-24 and 29-38 are directed to a transdifferentiated cell of epidermal origin and cultured in vitro, having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal or glial cell. Claim 28 relates to a cell culture derived from the transdifferentiated cell of Claim 17, and Claim 39 relates to a cell culture derived from the transdifferentiated cell of Claim 29. Claims 43-45 and 47 are directed to a kit for transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal or glial cell.

Applicant's Amendment

Applicant has amended Claim 1 merely to clarify further which of the previously Markush-listed cell markers are associated with the presence of which signal molecules listed in the Markush group of lines 2-5 of step (d). In addition, in Claim 1 (d)(ii), as now amended, a morphological feature has been added to the cells exhibiting neuronal cell markers, which feature "comprises one or more morphological neurite-like process(es) at least 50 micrometers in length." The specification discloses that neurons or neuron-like cells may express neurites, or neurite-like processes, longer than three cell diameters (about 50 microns or longer)(e.g., at page 5, lines 24-29; page 15, lines 16-19; and at page 18, lines 18-21), which morphological features are characteristic of neurons, but not of neural progenitor cells or glial cells.

Support for the amendment of Claim 1(d)(i) is found in the specification as originally filed, e.g., at page 16, lines 8-19.

Support for the amendment of Claim 1(d)(ii) is found in the specific as originally filed, e.g., at page page 13, lines 28-29; page 14, lines 2-6; page 16, lines 2-6 and 25-28; page 17, lines 17-21; and at page 26, line 26 through page 27, line 9, and Table 1, at page 29.

Support for the amendment of Claim 1(d)(iii) is found in the specific as originally filed, e.g., at page 16, lines 2-6; and page 17, lines 7-11.

Claim 15 has been amended merely to change the dependency from Claim 14, which was previously canceled, to pending Claim 1, from which canceled Claim 14 originally depended.

New Claim 49 is supported, e.g., by Claim 1, as originally filed and in the specification as originally filed, e.g., at page page 13, lines 28-29; page 14, lines 2-6; page 16, lines 2-6 and 25-28; page 17, lines 17-21; and at page 26, line 26 through page 27, line 9, and Table 1, at page 29.

New Claim 50 is supported, e.g., by Claim 2, as originally filed.

New Claim 51 is supported, e.g., by Claim 3, as originally filed.

New Claim 52 is supported, e.g., by Claim 4, as originally filed.

New Claim 53 is supported, e.g., by Claim 5, as originally filed.

New Claim 54 is supported, e.g., by Claim 6, as originally filed.

New Claim 55 is supported, e.g., by Claim 7, as originally filed.

New Claim 56 is supported, e.g., by Claim 8, as originally filed.

New Claim 57 is supported, e.g., by Claim 9, as originally filed.

New Claim 58 is supported, e.g., by Claim 10, as originally filed.

New Claim 59 is supported, e.g., by Claim 11, as originally filed.

New Claim 60 is supported, e.g., by Claim 15, as originally filed.

New Claim 61 is supported, e.g., by Claim 17, as originally filed.

New Claim 62 is supported, e.g., by Claim 19, as originally filed.

New Claim 63 is supported, e.g., by Claim 22, as originally filed.

New Claim 64 is supported, e.g., by Claim 23, as originally filed.

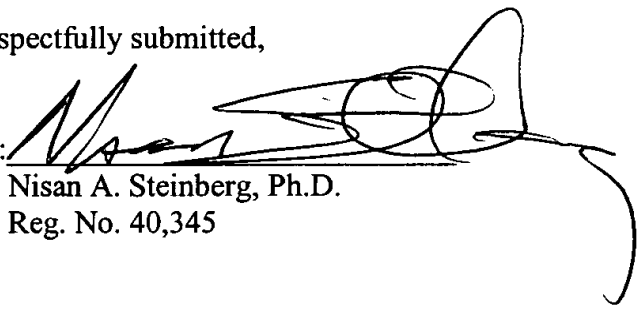
New Claim 65 is supported, e.g., by Claim 27, as originally filed.

New Claim 66 is supported, e.g., by Claim 28, as originally filed.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,

By: 

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Version with Markings to Show Changes Made

In the Claims:

Please amend Claims 1 and 15, and add new claims 49-66, as follows.

1. (Thrice Amended) An in vitro method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell, comprising:

(a) culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s), said cell(s) derived from the skin of a mammalian subject;

(b) exposing the cell(s) to an amount of an antagonist of bone morphogenetic protein (BMP) effective to antagonize endogenous BMP signal transduction activity;

(c) growing the cell(s) in the presence of at least one antisense oligonucleotide comprising a segment of a human MSX1 gene and/or a segment of a human HES1 gene, or homologous non-human counterpart of either of these, in an amount effective to suppress the expression of functional gene product of MSX1 and/or HES1, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell; and

(d) growing the transdifferentiated cell in a medium comprising a retinoid compound and a signal molecule selected from the group consisting of brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), platelet-derived growth factor (PDGF), nerve growth factor (NGF), neurotrophin (NT)-3, neurotrophin (NT)-4, IL-6, sonic hedgehog, and sonic hedgehog aminoterminal peptide, [and wherein the physiological and/or immunological feature comprises expression of a marker selected from the group consisting of nestin, neural RNA-binding protein Musashi, neurofilament M, neural-specific β-tubulin, neural-specific enolase, microtubule associated protein 2, glial fibrillary acidic protein (GFAP), O4, or a combination of any of these] wherein:

(i) said signal molecule, being selected from the group consisting of sonic

hedgehog and sonic hedgehog aminoterminal peptide, the physiological and/or immunological feature comprises expression of a neural progenitor cell marker selected from the group consisting of nestin and neural RNA-binding protein Musashi, or a combination of these;

(ii) said signal molecule, being selected from the group consisting of brain-derived neurotrophic factor (BDNF), platelet derived growth factor (PDGF), nerve growth factor (NGF), sonic hedgehog, sonic hedgehog aminoterminal peptide, neurotrophin (NT)-3, and neurotrophin (NT)-4, the physiological and/or immunological feature comprises expression of a neuronal cell marker selected from the group consisting of neurofilament M, neural-specific β-tubulin, neural-specific enolase, and microtubule associated protein 2, or a combination of any of these; and wherein the morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length; and

(iii) said signal molecule, being selected from the group consisting of ciliary neurotrophic factor (CNTF), IL-6, sonic hedgehog, and sonic hedgehog aminoterminal peptide, the physiological and/or immunological feature comprises expression of a glial cell marker selected from the group consisting of glial fibrillary acidic protein (GFAP) and O4.

2. (Reiterated) The method of Claim 1, wherein the subject is a human.

3. (Reiterated) The method of Claim 1, wherein the epidermal basal cell(s) is derived from a skin biopsy.

4. (Reiterated) The method of Claim 1, wherein culturing the proliferating epidermal basal cell population further comprises separating keratinized epidermal cells from the epidermal basal cells in a calcium-free medium.

5. (Reiterated) The method of Claim 1, wherein the amount of the antagonist of bone morphogenetic protein is about 10^{-6} to 10^{-4} M.

6. (Reiterated) The method of Claim 5, wherein the amount of the antagonist of bone morphogenetic protein is about 5 x 10^{-6} to 5 x 10^{-5} M.

7. (Reiterated) The method of Claim 1, wherein the antagonist of bone morphogenetic protein (BMP) is fetuin, noggin, chordin, gremlin, or follistatin.

8. (Reiterated) The method of Claim 7, wherein the fetuin is mammalian or avian fetuin.

9. (Reiterated) The method of Claim 8, wherein the mammalian fetuin is human, bovine, porcine, ovine, or equine fetuin.

10. (Reiterated) The method of Claim 1, wherein the antisense oligonucleotide(s) is modified with one or more thio groups.

11. (Reiterated) The method of Claim 1, wherein the amount of the antisense oligonucleotide is about 5 x 10^{-6} M to about 10^{-5} M.

13. (Reiterated) The method of Claim 1, wherein the morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length.

15. (Amended) The method of Claim 1[4], wherein the retinoid compound is all-trans retinoic acid or Vitamin A.

17. (Reiterated) A transdifferentiated cell of epidermal origin having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell produced by the method of Claim 1.

19. (Reiterated) The transdifferentiated cell of Claim 17, wherein the cell further exhibits a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

20. (Reiterated) The cell of Claim 17, wherein the transdifferentiated cell has a morphological, physiological and/or immunological feature specific to a neuronal cell.

22. (Reiterated) The transdifferentiated cell of Claim 20, wherein the cell is a GABAergic cell.

23. (Reiterated) The transdifferentiated cell of Claim 20, wherein the cell is a dopaminergic cell.

24. (Reiterated) The transdifferentiated cell of Claim 17, wherein the morphological feature comprises one or more neurite-like process(es) at least about 50 micrometers in length.

25. (Reiterated) The cell of Claim 17, wherein the transdifferentiated cell has a morphological, physiological, or immunological feature specific to an astroglial or oligodendroglial cell.

26. (Reiterated) The transdifferentiated cell of Claim 25, wherein the

immunological feature comprises expression of glial fibrillary acidic protein (GFAP) or O4.

27. (Reiterated) The transdifferentiated cell of Claim 17, wherein the cell is of human origin.

28. (Reiterated) A cell culture derived from the transdifferentiated cell of Claim 17, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell.

29. (Reiterated) A transdifferentiated cell of epidermal origin and cultured in vitro, comprising a cell of epidermal basal cell origin, said transdifferentiated cell displaying one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell, wherein the physiological and/or immunological feature comprises expression of a marker selected from the group consisting of nestin, neural RNA-binding protein Musashi, neurofilament M, neural-specific β-tubulin, neural-specific enolase, microtubule associated protein 2, glial fibrillary acidic protein (GFAP), O4, or a combination of any of these.

30. (Reiterated) The transdifferentiated cell of Claim 29, wherein the cell further displays the physiological feature of a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

31. (Reiterated) The cell of Claim 29, wherein the transdifferentiated cell has a morphological, physiological, or immunological feature specific to a neuronal cell.

32. (Reiterated) The transdifferentiated cell of Claim 31, wherein the physiological and/or immunological feature comprises expression of neural RNA-binding protein Musashi, neurofilament M, neural-specific β-tubulin, neural-specific enolase, microtubule associated

protein 2.

33. (Reiterated) The transdifferentiated cell of Claim 31, wherein the cell is a GABAergic cell.

34. (Reiterated) The transdifferentiated cell of Claim 31, wherein the cell is a dopaminergic cell.

35. (Reiterated) The transdifferentiated cell of Claim 29, wherein the morphological feature comprises one or more neurite-like process(es) at least about 50 micrometers in length.

36. (Reiterated) The transdifferentiated cell of Claim 29, wherein the cell is of human origin.

37. (Reiterated) The cell of Claim 29, wherein the transdifferentiated cell has a morphological, physiological, or immunological feature specific to an astroglial or oligodendroglial cell.

38. (Reiterated) The transdifferentiated cell of Claim 37, wherein the physiological and/or immunological feature comprises expression of glial fibrillary acidic protein (GFAP) or O4.

39. (Reiterated) A cell culture derived from the transdifferentiated cell of Claim 29, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell.

43. (Reiterated) A kit for transdifferentiating, in vitro, an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell, comprising:

(A) an antagonist of bone morphogenetic protein (BMP);

(B) at least one antisense oligonucleotide comprising a segment of a human MSX1 gene, a segment of a human HES1 gene, or a non-human homologous counterpart of either of these; and

(C) a retinoid compound and a signal molecule selected from the group consisting of brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), platelet-derived growth factor (PDGF), nerve growth factor (NGF), neurotrophin (NT)-3, neurotrophin (NT)-4, IL-6, sonic hedgehog, and sonic hedgehog aminoterminal peptide.

44. (Reiterated) The kit of Claim 43, further comprising instructions for using (A), (B), and (C) in transdifferentiating a subject's epidermal basal cell(s).

45. (Reiterated) The kit of Claim 43, wherein the antagonist of bone morphogenetic protein (BMP) is fetuin, noggin, chordin, gremlin, or follistatin.

47. (Reiterated) The kit of Claim 43, wherein the retinoid compound is all-trans retinoic acid or Vitamin A.

Please Add New Claims 49-65 as follows:

--49. (New) An in vitro method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell, comprising:

(a) culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s), said cell(s) derived from the skin of a mammalian subject;

(b) exposing the cell(s) to an amount of an antagonist of bone morphogenetic protein (BMP) effective to antagonize endogenous BMP signal transduction activity;

(c) growing the cell(s) in the presence of at least one antisense oligonucleotide comprising a segment of a human MSX1 gene and/or a segment of a human HES1 gene, or homologous non-human counterpart of either of these, in an amount effective to suppress the expression of functional gene product of MSX1 and/or HES1, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell; and

(d) growing the transdifferentiated cell in a medium comprising a retinoid compound and a signal molecule selected from the group consisting of brain-derived neurotrophic factor (BDNF), platelet-derived growth factor (PDGF), nerve growth factor (NGF), neurotrophin (NT)-3, neurotrophin (NT)-4;

wherein the physiological and/or immunological feature comprises expression of a neuronal cell marker selected from the group consisting of neurofilament M, neural-specific β-tubulin, neural-specific enolase, and microtubule associated protein 2, or a combination of any of these; and

wherein the morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length.

50. (New) The method of Claim 49, wherein the subject is a human.

51. (New) The method of Claim 49, wherein the epidermal basal cell(s) is derived from a skin biopsy.

52. (New) The method of Claim 49, wherein culturing the proliferating epidermal

basal cell population further comprises separating keratinized epidermal cells from the epidermal basal cells in a calcium-free medium.

53. (New) The method of Claim 49, wherein the amount of the antagonist of bone morphogenetic protein is about 10^{-6} to 10^{-4} M.

54. (New) The method of Claim 53, wherein the amount of the antagonist of bone morphogenetic protein is about 5×10^{-6} to 5×10^{-5} M.

55. (New) The method of Claim 49, wherein the antagonist of bone morphogenetic protein (BMP) is fetuin, noggin, chordin, gremlin, or follistatin.

56. (New) The method of Claim 55, wherein the fetuin is mammalian or avian fetuin.

57. (New) The method of Claim 56, wherein the mammalian fetuin is human, bovine, porcine, ovine, or equine fetuin.

58. (New) The method of Claim 49, wherein the antisense oligonucleotide(s) is modified with one or more thio groups.

59. (New) The method of Claim 49, wherein the amount of the antisense oligonucleotide is about 5×10^{-6} M to about 10^{-5} M.

60. (New) The method of Claim 49, wherein the retinoid compound is all-trans retinoic acid or Vitamin A.

61. (New) A transdifferentiated cell of epidermal origin having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell produced by the method of Claim 49, wherein the physiological and/or immunological feature comprises expression of a marker selected from the group consisting of neurofilament M, neural-specific β-tubulin, neural-specific enolase, and microtubule associated protein 2, or a combination of any of these; and wherein the morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length.

62. (New) The transdifferentiated cell of Claim 61, wherein the cell further exhibits a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

63. (New) The transdifferentiated cell of Claim 61, wherein the cell is a GABAergic cell.

64. (New) The transdifferentiated cell of Claim 61, wherein the cell is a dopaminergic cell.

65. (New) The transdifferentiated cell of Claim 61, wherein the cell is of human origin.

66. (New) A cell culture derived from the transdifferentiated cell of Claim 61, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a neuronal cell.--.